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Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery

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Editor's key points

- The perioperative use of colloid solutions has potential benefits in cardiac surgical patients, but may affect coagulation.
- In this randomized study of 240 patients, the use of high volumes of colloid (50 ml kg^{-1} day^{-1}) had no effect on the primary outcome measure, blood loss from chest drains.
- However, blood transfusion requirements were lower when a crystalloids-only fluids regimen was used.
- The infusion of high volumes of colloids caused more haemodilution and had greater adverse effects on coagulation.

Background. Infusion of 5% human albumin (HA) and 6% hydroxyethyl starch 130/0.4 (HES) during cardiac surgery expand circulating volume to a greater extent than crystalloids and would be suitable for a restrictive fluid therapy regimen. However, HA and HES may affect blood coagulation and could contribute to increased transfusion requirements.

Methods. We randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml kg^{-1} day^{-1} of either HA, HES, or Ringer's lactate (RL) as the main infusion fluid perioperatively. Study solutions were supplied in identical bottles dressed in opaque covers. The primary outcome was chest tube drainage over 24 h. Blood transfusions, thromboelastometry variables, perioperative fluid balance, renal function, mortality, intensive care unit, and hospital stay were also assessed.

Results. The median cumulative blood loss was not different between the groups (HA: 835, HES: 700, and RL: 670 ml). However, 35% of RL patients required blood products, compared with 62% (HA) and 64% (HES group; $P=0.0003$). Significantly, more study solution had to be administered in the RL group compared with the colloid groups. Total perioperative fluid balance was least positive in the HA group [6.2 (2.5) litre] compared with the HES [7.4 (3.0) litre] and RL [8.3 (2.8) litre] groups ($P<0.0001$). Both colloids affected clot formation and clot strength and caused slight increases in serum creatinine.

Conclusions. Despite equal blood loss from chest drains, both colloids interfered with blood coagulation and produced greater haemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.

Keywords: blood loss; coagulation; colloids; fluid regime; Ringer's lactate; rotation thromboelastometry; transfusion

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Controversy exists about the optimal perioperative fluid management in patients undergoing major surgery. Prevention of fluid overload intraoperatively has been associated with less postoperative complications.[1] In addition, the transfusion of packed red blood cells (PRBCs) is associated with increased morbidity and mortality after cardiac surgery.[2] Thus, avoiding transfusion might also be important to improve outcome of patients undergoing cardiac procedures.

Crystalloids, in the form of Ringer's lactate (RL), and colloids such as hydroxyethyl starches and 5% human serum albumin (HA) are commonly used for intraoperative fluid management during heart surgery. The latter two have a more profound volume expansion effect than crystalloids and would therefore be more suitable for a restrictive fluid therapy.[3] However, hydroxyethyl starch solutions have been shown to impair coagulation[4 5] and renal function.[6–11] Six per cent hydroxyethyl starch 130/0.4 [Voluven®] (HES) is a newer generation tetrastarch formulation with a lower molecular weight, which might affect coagulation to a lesser degree than hydroxylethyl starch solutions with higher molecular weight.[12–15] However, a recent meta-analysis stated that insufficient data are available for the effect of HES on the bleeding tendency in cardiac patients.[16] In comparison with HES, HA has been used since the 1970s during cardiac surgery mainly for two reasons: first, HA is able to coat the fluid pathway surface and thereby reduces platelet activation and consumption with concomitant release of inflammatory mediators.[3 17–19] Secondly, HA prevents a substantial decrease in colloid oncotic pressure.[20] Likewise, RL has also been used for many years during heart surgery, either as the sole replacement fluid or in

combination with HA or HES.[21] Since large volumes are generally administered throughout the procedure, even RL might influence coagulation via dilution of coagulation factors.

We hypothesized that 6% HES 130/0.4 would increase blood loss from the chest drains. Thus, the main objective of our study was to compare external blood loss from chest drains between groups receiving HA 5%, 6% HES 130/0.4, or RL as the main infusion during cardiac surgery. Blood transfusions, total perioperative fluid balance, thromboelastometry variables, course of serum creatinine and platelet count, intubation time, intensive care unit (ICU), and hospital stay were also assessed.

Methods

Participants

This randomized, double-blind, single-centre trial, which was conducted over the course of four consecutive years at our department was approved by the institutional review board and reported to the national regulatory authority (Gov Identifier: NCT 01174719). All 240 patients provided written informed consent before inclusion. Inclusion criteria were: patients undergoing elective cardiovascular surgery [i.e. coronary artery bypass grafting (CABG), valve repair or replacement, and surgery of the ascending aorta] on cardiopulmonary bypass (CPB). Exclusion criteria were known allergy to hydroxyethyl starch or albumin, preoperative anaemia, emergencies, treatment with acetylsalicylic acid <3 days before surgery, GPIIbIIIa antagonists use <7 days before surgery, coagulation disorders [i.e. INR >1.2, activated partial thromboplastin time (aPTT) >40 s, platelet count <100 g litre^{-1}], BMI >40 kg m^{-2}, left ventricular ejection fraction $<20\%$, renal dysfunction defined as serum creatinine >1.5 mg dl^{-1}, proven heparin-induced thrombocytopenia, and danaparoid or lepirudin treatment during the month before the operation.

Randomization, fluid regimen, and blinding

Eligible patients were randomized into three groups comprising 80 patients each with the following fluid regimens:

HA group: 5% albumin up to 50 ml kg^{-1} day^{-1}, additional RL as required;
HES group: 6% HES 130/0.4 up to 50 ml kg^{-1} day^{-1}, additional RL as required;
RL group: RL up to 50 ml kg^{-1} day^{-1}, additional RL as required.

An independent IT specialist was in charge of randomization, which was performed using a random number generator. The local pharmacy prepared the study solutions that were supplied in identical 250 ml bottles. Blinding was performed with the help of opaque covers that were placed around the bottles and the infusion sets.

Procedures

Anaesthesia was induced with midazolam (0.1 mg kg^{-1}), propofol (1.0–1.5 mg kg^{-1}), fentanyl (3–10 μg kg^{-1}), and cisatracurium (0.2 mg kg^{-1}) and maintained with sevoflurane (target BIS value 40–50), and fentanyl (0.05–0.1 μg kg^{-1} min^{-1}). Fluid administration was started with 250–500 ml of the study solution during induction of anaesthesia. The CPB circuit was primed with 1500 ml study solution together with 5000 IE heparin, and 100 ml mannitol 20%. Patients received either aprotinin (10^6 IU after anaesthesia induction plus 10^6 IU added to the CBP prime) or tranexamic acid (either 1.0 or 1.5 g after anaesthesia induction plus the same dosage in the CPB prime according to the patient's body weight and renal function). Tranexamic acid was used as antifibrinolytic after November 2007 when sale of aprotinin was suspended by Bayer. After anticoagulation with heparin (300 IE kg^{-1}) and achieving an activated clotting time (ACT) >400 s, CPB was performed using non-pulsatile flow at 2.5 litre min^{-1} m^{-2}, a non-heparin-coated circuit, and a membrane oxygenator (Quadrox™, Maquet, Hirrlingen, Germany, or Dideco Compactflow™, Mirandola, Italy). Mild-to-moderate hypothermia was induced (30–34°C) and norepinephrine was given if necessary to maintain a mean arterial pressure $>$ 60 mm Hg. Buckberg cardioplegic solution was used for myocardial preservation. Additional RL was added to the extracorporeal circuit when filling of the CPB reservoir was insufficient. During and after weaning from CPB, transoesophageal echocardiography was used to monitor myocardial performance and the impact of fluid loading and inotropic support on ventricular function. Further fluid management and also vasopressors and/or inotropic use was at the discretion of the attending consultant and not controlled by protocol. All study cases were performed by experienced cardiac anaesthesia fellows supervised by senior cardiac anaesthesiologists. Intraoperative fluid therapy with study solution was restricted to two-thirds of the maximally allowed daily dose (i.e. 33.3 ml kg^{-1}). It was assumed that anaesthesia and surgery would require a greater fluid load than the immediate postoperative period. Additional fluid requirements were met with RL in order to avoid accidental overdosage of either of the two colloids. The last third of the study solution (i.e. 16.7 ml kg^{-1}) was kept for the initial volume replacement in the ICU that also guaranteed that the total permitted dose would not be administered within a short period of time.

Rotation thromboelastometry (ROTEM® Pentapharm CO, Munich, Germany) *ex vivo* coagulation variables were examined using predefined tests: INTEM (ellagic acid activated intrinsic pathway) and FIBTEM (with platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation).[22] The samples were analysed within 120 s after blood was drawn from the central venous catheter and coagulation was initiated with activators using a semi-automated electronic pipette system according to the manufacturer's instructions. Coagulation was allowed to proceed for 50 min. Automatic ROTEM variables were: clotting time (CT), clot formation time (CFT), α-angle, maximum clot firmness (MCF), and clot lysis. These variables have been validated using standard coagulation tests.[22 23] ROTEM quality control measures were undertaken weekly by our laboratory staff. Reference ranges for ROTEM thromboelastometry variables were taken from a multi-centre investigation.[24]